REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 59-93 will be active in the application subsequent to entry of this Amendment.

Applicant is pleased to note that the method claims have been rejoined and thanks the examiner for the courtesies and information extended during the interview of May 17, 2007. The main issue raised in the outstanding Official Action is the rejection of all pending claims under 35 USC §103(a) as being unpatentable/"obvious".

The rejection is based on six newly cited prior art references (two are identified on page 2 of the specification). The objection to the composition claims is based on four different citations (*see* the sixth to third from last lines on page 4 of the Office Action). The objection to the process claims is based on five different citations (*see* the last two paragraphs on page 6 and the whole of page 7 of the Office Action).

However, as the US courts have stated, that the fact that it is necessary to cite such a large number of references is, in and of itself, indicative of non-obviousness. *Minneapolis-Honeywell Regulator Company v. Midwestern Instruments, Inc.*, 298 F.2d 36, 38, 131 U.S.P.Q. 402, 403 (7th Cir. 1961); *The Ric-Wil Company v. E.B. Kaiser Company*, 179 F.2d 401, 404, 84 U.S.P.Q. 121, 124 (7th Cir. 1950); *Reynolds et al v. Whitin Machine Works*, 167 F.2d 78, 83, 76 U.S.P.Q. 551, 555 (4th Cir. 1948); and *Racal-Vadic, Inc. v. Universal Data Systems*, 1980 U.S. Dist. LEXIS 15864, *81, 207 U.S.P.Q. 902, 927 (N.D. Ala. 1980).

As regards the specific objection raised by the Examiner, a key aspect is the Examiner's assertion that the skilled person would have thought it was obvious to use PG, BHA and BHT in the same way as benzyl alcohol and phenyl ethanol are used in '486. More specifically, the Examiner suggests (*see* e.g. the last paragraph on page 7 of the Office Action) that in view of the prior art, it is predictable that all aromatic alcohols enhance the absorption of macromolecules. With respect, the applicant simply cannot accept this suggestion.

A skilled person would not have expected the aromatic alcohols used in claim 59 to enhance the absorption of macromolecules

Firstly, the Examiner's assertion is even contradicted by the very prior art cited in the Office Action. For instance, at column 1 line 59 to column 2 line 5 of Wacher '522 it is

explained that the utility of a given compound in enhancing the absorption of drugs is very unpredictable, even within a given class of compounds.

The aromatic alcohols used in the present application should not even be considered to be in the same class as benzyl alcohol, phenoxy ethanol and phenyl ethanol of New '436. That is because there are fundamental differences between the '436 compounds and the alcohols used in claim 59. For instance, significant differences in the solubility, hydrophilicity and the physical forms of the compounds have already been explained in previous response, *see* e.g. pages 12 and 13 of the pages accompanying the RCE filed on November 27, 2007.

Thus, the '436 compounds are a class of hydrophilic water-soluble compounds that are liquid at room temperature. BHA, BHT and PG, on the other hand, are part of a class of compounds that are solid at room temperature and have very poor solubility in water. These differences were explained in the application as filed (*see* e.g. page 1 lines 9-15 and page 2 lines 6-8) and are also supported by the documentary evidence filed with the RCE on November 27, 2007.

Given that it is known from '522 that the ability of compounds to enhance the absorption of macromolecules cannot even be predicted within a given class of compounds, clearly it is even less predictable when comparing compounds of different classes.

Furthermore, there are many aromatic alcohols for which no such absorption enhancing activity across the intestine has been found. Examples of such agents include, for instance, natural products that play an important role in biochemical processes, such as tyrosine, vitamin E, pyridoxine and nucleosides.

Moreover, many pharmaceutical agents that fall within the genus of aromatic alcohols have such poor oral bioavailability themselves, that research work has been specifically undertaken to combine them with known permeation enhancers in order to increase their absorption up to acceptable levels. Examples of such compounds are sampatrilat (compound UK 81252)[1], acyclovir[2] and doxorubicin[3]. 1. Evidence for the research being carried out for these compounds may be found in the following scientific papers, attached:

[1] Rong-Kun Chang & Amir H Shojaei, *Effect of a lipoidic excipient on the absorption profile of compound UK 81252 in dogs after oral administration.* J Pharm Pharmaceut Sci 7(1):8-12, (2004)

[2] Attia IA, El-Gizawy SA, Fouda MA & Donia AM, *Influence of a Niosomal Formulation on the Oral Bioavailability of Acyclovir in Rabbits.* AAPS Pharm. Sci. Tech. 8(4): Article 106 (2007)

[3] Ke W, Zhao Y, Huang R, Jiang C & Pei Y, *Enhanced Oral Bioavailability of Doxorubicin in a Dendrimer Drug Delivery System.* J Pharm Sci. 97(6):2208-16 (2008).

Thus, there are many aromatic alcohols which themselves lack bioavailability, let alone have any ability to enhance the bioavailability of any other compounds, such as macromolecules.

Against this background it is not credible to suggest that simply because three aromatic alcohols from document '436 - namely benzyl alcohol, phenoxy ethanol and phenyl ethanol - can enhance the absorption of macromolecules in the intestines, it follows that all aromatic alcohols would have this effect.

Accordingly, no skilled person would have contemplated using BHA, BHT or PG in a pharmaceutical composition for the purpose of enhancing the absorption of macromolecules. Rather, regardless of their overall aim, if a skilled person had contemplated adding PG, BHA and/or BHT to a pharmaceutical composition of any kind, the only function of these compounds that they would have had in mind is their known function as antioxidants.

To this end, common general knowledge and/or routine optimization of the quantities would have led inevitably to the use of a low concentration. This is explained in the very prior art the Examiner has cited in the Office Action, *see* e.g. column 4 lines 44 to 45 of Wacher '666. Thus, if using PG, BHA and/or BHT, it is obvious to employ them in the low concentrations at which they are known to be used, and using the much higher concentration required by claim 59 would have been non-obvious.

In view of the above comments it is believed that the Examiner's obviousness objection should be withdrawn. Notwithstanding this, there are further aspects of the Examiner's objection that the applicant respectfully disagrees with, including the following points.

The mention of cyclic peptides in Wacher's '522 and '666 does not suggest that the alcohols in question might be used to enhance the absorption of an active macromolecular principle

In '522 and '666 it is clear that cyclic peptides are not referred to in the context of macromolecules. Cyclic peptides found in nature, or used therapeutically, generally have an amino acid content of around ten, and certainly no more than twenty. Due to their relatively small size they are not considered to be proteins or polypeptides. This is important because it means they are easily able to pass across a cell membrane and directly into the cytoplasm. That is especially true if, like cyclosporine (the only cyclic peptide mentioned in '522 and '666), they are hydrophobic.

Once inside the cell these cyclic peptides, which are oligopeptides, will become the target of cytochrome P450, and the authors of '522 and '666 explain how this activity can be demonstrated, *see* e.g. col.8 lines 40-45 of '666, where an article by another author - Watkins - is said to provide the details for the method envisaged.

Thus, the cyclic peptides discussed in '522 and '666 must be able to pass through the cell membrane. However, macromolecules such as proteins and polypeptides – being larger than oligopeptides - are unable to pass into cells unaided. Indeed, this was explained in the application as filed (*see* the middle paragraph on page 2). This confirms that the reference in '522 and '666 to cyclic peptides cannot be referring to macromolecules. Thus, it is evident that the authors of '522 and '666 could not have seen any possibility of applying their technology to polypeptides, proteins and macromolecules in general.

This is further reinforced by the fact that cyclosporine is the only cyclic peptide mentioned in '522 and '666. Cyclosporine contains 11 amino acid residues. It is defined as 'a cyclic oligopeptide immunosuppressant ...' by dictionary.webmd.com (*see* the link: http://dictionary.webmd.com/terms/cyclosporine.xml). Its classification as an oligopeptide is also confirmed by the 13th edition of the Merck Index, a copy of the relevant page of which is attached. Thus, macromolecules such as polypeptides and proteins were not contemplated by the authors of '522 and '666.

As a final comment on cyclosporin, it may be worthy of note that it has an unusual amino acid residue containing a carbon-carbon double bond, and it is this which is probably the target

of cytochrome P450. Since this residue does not exist in normal proteins or peptides, this is another reason why the mention of cyclosporin in '522 and '666 cannot be used to extrapolate to all peptides and proteins.

The Examiner's reference to the use of buffers and pH as part of the skilled person's thinking in arriving at the invention is not sound.

In '748 sodium bicarbonate is used to buffer pH to 7.5 to 9 (*see* e.g. abstract). Sodium bicarbonate has a pKa of 6.3. Compare this to, for example, one of the aromatic alcohols used in the present application, PG. PG has a pKa of 8.11. The pKa scale is, of course, a logarithmic scale. Accordingly, the disassociation constant for sodium bicarbonate is over 60 times greater than that for PG. Firstly, such a large difference in the degree of dissociation between the two compounds would put a skilled person off the idea of using PG as a mere replacement for sodium bicarbonate. However, on top of this PG has never been described or even suggested as an acidity adjuster in pharmaceutical practice.

Further, sodium bicarbonate, an inorganic compound, and the aromatic alcohol additives of claim 59 are chemically completely different. This would clearly make PG an undesirable choice to replace sodium bicarbonate.

Consider, for instance, the differences between the solubility of the additives of present claim 59 compared to that of the additive sodium bicarbonate used in '748. This is particularly relevant because the Examiner's reasoning seems to rely on it being obvious to use the additives of the present invention as buffers, and solubility is naturally an essential property for a buffer compound.

It is well known by any person (let alone a skilled chemist) that sodium bicarbonate is highly soluble in water. As already noted, however, the additives for use in compositions of the present invention are, in stark contrast, very poorly soluble in water. Not least, this is due to the hydrophobic terminal alkyl groups present in the additives used in the present invention. This was of course already explained in the comments accompanying the RCE filed on November 27, 2007.

Against this background it is simply not credible to suggest that a skilled person would consider using the additives defined in claim 59 in place of sodium bicarbonate used in New '748, let alone with any expectation of retaining the activity seen for the '748 compositions.

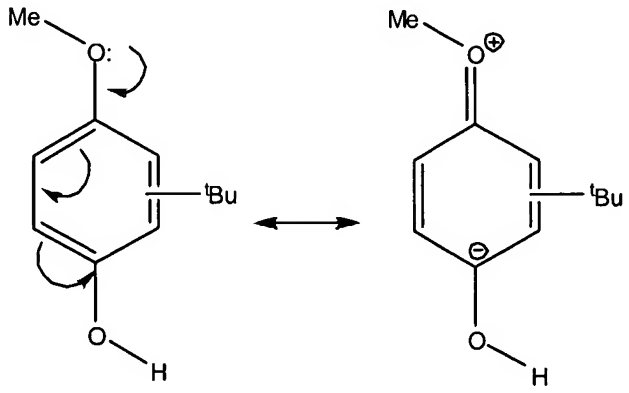
Incidentally, it is of note that New ('748) does not mention whether the compositions it discloses could (even optionally) contain antioxidants. In particular, there is no suggestion that even a small amount of any of the additives as defined in present claim 59 could be used.

The considerations noted above for PG also apply to BHA and BHT, but even more so because these have a pKa which is higher than PG. Evidence for this is provided by the attached copy of a US EPA report entitled "Alkylphenols Category (SECTION ONE) Development of Categories and Test Plans". This states (page 5, third paragraph from bottom) that

> "*...a review of the physical chemistry properties of substituted phenols confirms a limited pKa range of 9.9 to 10.9. Thus, none of the alkylphenols will be ionized significantly to environmental or physiological pH...*"

BHT is a phenol moiety with alkyl substituents so clearly falls within the genus "alkylphenols".

As for BHA, this features a methoxy (MeO-) group *para* to the phenolic –OH group. It is well known that a MeO- substituent on a benzene ring increases the electron density at the *para* position. This is due to conjugation with the aromatic ring wherein a lone pair of the oxygen atom (of the MeO- group) delocalizes into the benzene ring to produce various resonance forms, e.g. as depicted here:



The increase in electron density at the carbon atom to which the hydroxy group is attached enhances the positive inductive effect of the benzene ring mentioned in the passage quoted above. That will make the H atom of the hydroxy group less likely to escape as H^+

because it would leave behind a negatively charged oxygen atom. Thus, the MeO- group in BHA will raise the pKa even higher.

In view of the above comments it is respectfully submitted that the idea of using a buffer would actually lead the skilled person away from using the aromatic alcohols of present of claim 59.

Withdrawal of the §103 rejection is requested because the claimed invention would not have been obvious to the ordinary skilled artisan at the time applicant made his invention.

Having responded to all of the issues raised in the outstanding Official Action, applicant submits that his claims are in condition for allowance and solicits an early Notice to that affect. The examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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